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PATENT

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Mary Jane DiPalma
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Mary Jane DiPalma
Signature of person mailing correspondence

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Junying Yuan *et al.*	Art Unit:	1626
Serial No.:	09/688,015	Examiner:	D'Souza, A.
Filed:	October 13, 2000		
Title:	SMALL MOLECULE INHIBITORS OF NECROSIS		

Assistant Commissioner of Patents
Washington, D.C. 20231

DECLARATION OF ALEXEI DEGTEREV 37 CFR §1.132

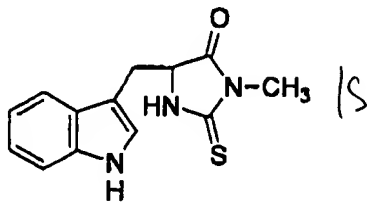
Under 37 C.F.R. § 1.132 and regarding the rejection of claims 9, 10, 17-25, 32-37, and 41 for lack of enablement, I declare:

1. I am an inventor of the subject matter described and claimed in the above-captioned patent application.

2. I hold a doctorate degree in Biochemistry from the Boston University and I have performed and directed research in the field of biochemistry for over four years.

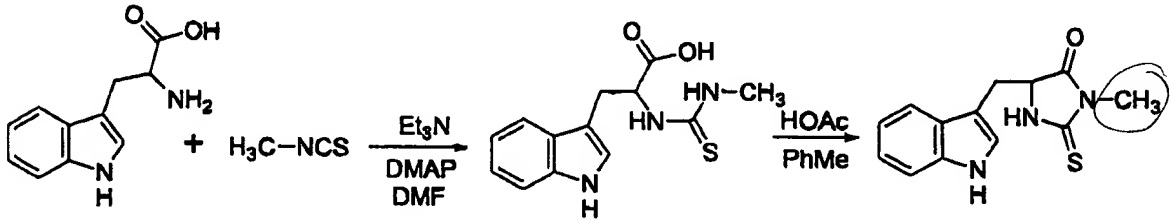
3. The chemical derivatives of Compound ID# 115807 that are the subject of the

rejected claims are easily and routinely prepared by a person of ordinary skill in organic and/or synthetic chemistry. Compound ID# 115807 (shown below) are known as thiohydantoin derivatives.



Compound ID # 115807

Compound ID # 115807, and compounds like it, have been synthesized for the purpose of sequencing proteins and peptides (see, for example, Edman, Acta Chem. Scand., 4: 283-293, 1950; Waterfield *et al.*, Biochemistry, 9: 832-839, 1970). Compounds of the present invention can be synthesized by reacting isothiocyanate with tryptophan, or a derivative thereof, followed by acid work up. This reaction, shown below for Compound ID# 115807, is often referred to as an "Edman degradation" when used in a sequencing context (see, Edman *ibid*).

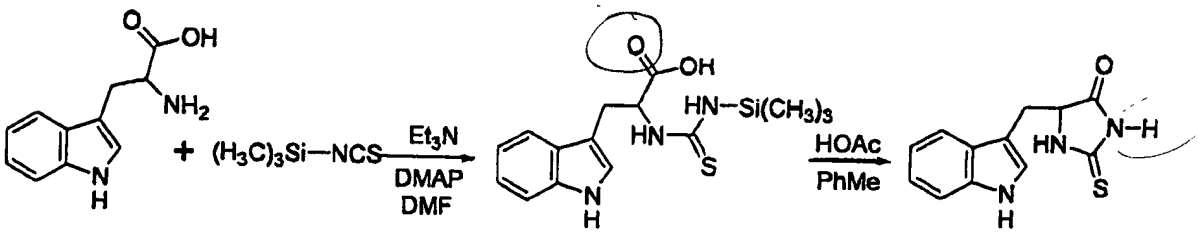


Tryptophan Compound ID# 115807

Reaction 1

As shown in reaction 2, unsubstituted thiohydantoin derivatives, corresponding to substitutions at the R4 position identified in the rejected claims, are made by substituting

trimethylsilyl isothiocyanate for methyl isothiocyanate. This chemical reaction scheme was disclosed, for example, in U.S. Patent No. 4,837,165 (issued June 6, 1989).



Reaction 2

Furthermore, the tryptophan rings, tryptophan methylene, tryptophan nitrogen and each of the thiohydantoin nitrogens can be substituted by starting with the appropriately substituted isothiocyanate and/or tryptophan. Examples of known tryptophan derivatives that can be used with these methods include 1-methyl-tryptophan (CAS 110117-83-4), 4-methyl-tryptophan (CAS 1954-45-6), 5-benzyloxy-tryptophan (CAS 6383-707-6), 5-bromo-tryptophan (CAS 6548-09-0), 5-fluoro-tryptophan (CAS 154-08-5), 5-hydroxy-tryptophan (CAS 103404-89-3), 5-methoxy-tryptophan (CAS 28052-84-8), 6-fluoro-tryptophan (CAS 7730-20-3), 6-methyl-tryptophan (CAS 2280-85-8), 7-benzyloxy-tryptophan (CAS 66866-40-8), and 7-methyl-tryptophan (CAS 17332-70-6), among others.

Alternatively, any of the amine nitrogens can be selectively substituted by, for example, an acyl or alkyl group. Such selective substitution can be achieved by protecting and deprotecting the unsubstituted amine functionalities if desired. Any number of such protecting groups are available in the art for this purpose. For example, commonly used protecting groups for amines include carbamates, such as *tert*-butyl, benzyl, 2,2,2 –trichloroethyl, 2-trimethylsilylethyl, 9-fluorenylmethyl, allyl, and m-nitrophenyl. Other commonly used protecting groups for amines include amides, such as

formamides, acetamides, trifluoroacetamides, sulfonamides, trifluoromethanesulfonyl amides, trimethylsilylethanesulfonamides, and *tert*-butylsulfonyl amides. Protecting groups can be chosen such that selective conditions (*e.g.*, acidic conditions, basic conditions, catalysis by a nucleophile, catalysis by a lewis acid, or hydrogenation) are required to remove each, exclusive of other protecting groups in a molecule. The conditions required for the addition of protecting groups to amine, alcohol, sulfhydryl, and carboxylic acid functionalities and the conditions required for their removal are provided, for example, in detail in T.W. Green and P.G.M. Wuts, Protective Groups in Organic Synthesis (2nd Ed.), John Wiley & Sons, 1991 and P.J. Kocienski, Protecting Groups, Georg Thieme Verlag, 1994.

Accordingly, the synthesis of the chemical compounds identified in the rejected claims was well within the capability of a person of ordinary skill in the art of organic and/or synthetic chemistry at the time the application was filed, using techniques and reagents known at the time.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

9/3/02
Date

Alexei Degterev, Ph.D.

\\Clark-w2k1\documents\00742\00742056003 Declaration by Alexei Degterev.wpd